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Zentiva, a.s., Prague, CZ

filed on December 7, 2004

an application of the invention – file No. **PV 2004-1192**

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Prague, December 16, 2004

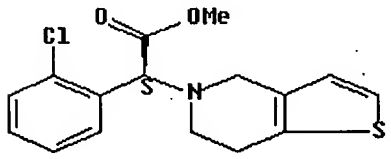
Method of producing crystalline clopidogrel hydrobromide

Technical Field

The invention relates to a method of producing the crystalline form of the hydrobromide of the (alpha S) alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester (hereinafter clopidogrel hydrobromide), designated as Form II, and to an intermediate useful for said method of producing, designated as Form III.

Background Art

The (alpha S) alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetic acid methyl ester, clopidogrel of formula I



I

is an anti-thrombic agent that was described in CZ patent 274 420 (EP 281 459), wherein blood coagulation decreasing activities of various salts of this substance were also demonstrated. Currently sold clopidogrel-based pharmaceutical formulations contain this active agent in the form of its hydrogensulfate salt (HSO_4^- anion). The method of preparation of the S-enantiomer, published in the above-cited patent involves reaction of the racemic mixture with optically active camphorsulfonic acid and subsequent separation of the diastereoisomer.

The respective salt of clopidogrel with camphorsulfonic acid is converted, by a solution of sodium hydrogen carbonate in methylene chloride medium, into an optically active base, which is obtained by evaporation of the solvent.

The evaporation residue of the active base is converted into the respective salt. Specifically, the hydrobromide is obtained by dissolving the base in diethyl or diisopropyl ether and

precipitating drop by drop with 48% hydrobromic acid. Drying the formed precipitate affords crystals with the melting point of 111 °C.

In the cited patent, toxicity of the hydrobromide is also evaluated, which is even somewhat lower than that of the currently used hydrogensulfate. (LD_{50} of clopidogrel hydrogen sulfate is 2,591 mg and LD_{50} of clopidogrel hydrobromide is 4,268 mg).

Disclosure of Invention

Form I of clopidogrel hydrobromide is characterized by interplanar distances ascertained by X-ray diffraction, d: 4.01 Å; 4.39 Å and 3.17 Å, or by infrared spectrogram with bands at 1743; 1421; 1237; 760 and 728 cm^{-1}.

The crystalline Form I can be obtained from a solution of the base in toluene by precipitating with 48% hydrobromic acid.

Form II of clopidogrel hydrobromide II is characterized by interplanar distances ascertained by X-ray diffraction, d: 4.52 Å; 3.83 Å; 3.48 Å, or by infrared spectrogram with bands at 1754; 1436; 1317 and 1223 cm^{-1}.

Form II can be obtained by reaction of a solution of the clopidogrel base in an organic solvent, e.g. ethyl acetate or toluene, with a solution of hydrobromic acid in toluene. This procedure, however, requires first preparing a solution of hydrogen bromide in toluene by introducing gaseous hydrogen bromide into the solvent and using this solution further.

A simpler method according to the present invention comprises preparation of Form II by introducing gaseous hydrogen bromide into a solution of clopidogrel base in an organic solvent, preferably in an aromatic C_6-C_{12} hydrocarbon, for example toluene. Preferably, hydrogen bromide is introduced at a lowered temperature, e.g., -15 °C to 30 °C, more preferably at a temperature lower than 10 °C; at this temperature, in a stirred solution, the crystalline Form II further matures. Usual time of stirring is 2 to 8 hours. A preferable concentration of the solution of the clopidogrel base is 15 to 40 weight % and the molar ratio of the clopidogrel base and hydrogen bromide is 1 : 0.9 to 1.1.

Form III can be prepared by a similar method, wherein, however, hydrogen bromide is introduced into a solution of clopidogrel having a concentration lower than 15 %, preferably 1 to 10 %. Hydrogen bromide is again introduced at a lowered temperature, for example -15 °C to 30 °C. Form III matures at a lower temperature by stirring for 2 to 8 hours.

Another aspect of the present invention is a new crystalline form III, which is characterized by the following peaks ascertained by X-ray diffraction at 2θ positions: 7.796 °; 15.380 °; 18.389 °; 19.369 ° and 23.895 °.

Form III can be used as an intermediate which is further processed into the pharmaceutically applicable Form II. This can be made by crystallization or precipitating an alcoholic solution of clopidogrel hydrobromide. Alcohols for said solution are selected from the series of C_1-C_5; 2-propanol being preferred. Another less polar solvent can be added to the solution, preferably an ether, ester or ketone. Methyl *tert*-butyl ether has turned out to be especially preferred. In this manner, Form II can be obtained in an especially high purity.

Melting points of all the forms are difficult to reproduce and identification fails. They range between about 113 and 145 °C.

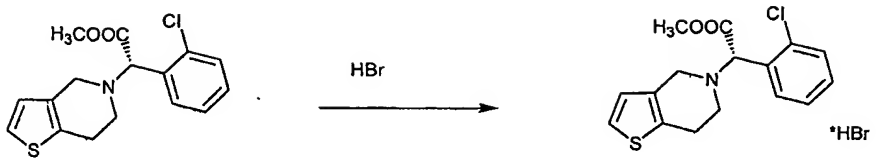
Brief Description of Drawings

Figure 1 shows an X-ray diffraction pattern of clopidogrel hydrobromide Form III.

Examples

The invention is illustrated by the following examples, which do not have a limiting character in any respect.

Scheme



(I) (II)

Example 1

203 g of the clopidogrel base (0.6308 mol) were dissolved in 1000 ml of toluene. With stirring, the solution was cooled down to 0 to +5 °C. Introduction of gaseous hydrogen bromide into the cooled solution was started. The pressure bomb was positioned on a balance and after 50 g of hydrogen bromide has gone, the introduction was stopped; its total duration was ca. 15 mins. The temperature while adding hydrogen bromide ranged between +5 and +10 °C. The thick reaction mixture was then stirred at 0 to -5 °C for 4 hrs. The resulting crystalline matter was sucked off through a filter glass and washed with 500 ml of toluene. Air drying afforded 243.7 g of clopidogrel hydrobromide.
An X-ray analysis proved the Form II. HPLC purity more than 99.0 %.

Example 2

260.7 g of the clopidogrel base (0.8101 mol) were dissolved in 2600 ml of toluene. With stirring, the solution was cooled down to 0 to +5 °C. Introduction of gaseous hydrogen bromide into the cooled solution was started. The pressure bomb was positioned on a balance and after 65 g of hydrogen bromide has gone, the introduction was stopped; its total duration was ca. 15 mins. The temperature while adding hydrogen bromide ranged between +5 and +10 °C. The thick reaction mixture was then stirred at 0 to -5 °C for 4 hrs. The resulting crystalline matter was sucked off through a filter glass and washed with 500 ml of toluene. Air drying afforded 368.5 g of clopidogrel hydrobromide.
The resulting crystalline product was characterized by an X-ray diffraction pattern as new Form III. HPLC purity more than 99.5 %.

The resulting crystals provided the following X-ray diffraction pattern:

2θ [°]	d [Å]	I_{rel}
7.796	11.332	100.00
10.457	8.453	12.63
10.987	8.046	12.80
12.408	7.128	16.05
15.380	5.757	25.30
18.389	4.821	35.42
19.369	4.579	33.25
20.616	4.305	14.13
21.807	4.072	19.17
22.569	3.937	13.33
23.170	3.836	15.10
23.291	3.816	15.72
23.895	3.721	28.41
24.052	3.697	12.75
25.489	3.492	12.04
25.735	3.459	12.72
28.744	3.103	12.40

Example 3

Clopidogrel hydrobromide of Example 2 (368.5 g) was dissolved while stirring in 2000 ml of 2-propanol at a temperature up to 60 °C. To this solution methyl *tert*-butyl ether (MTBE) was added (2135 ml) at 45 to 55 °C. The solution was slowly cooled down to room temperature (ca. 2 hrs); crystallization started. After 2 hours, the solution was cooled down to 0 to -5 °C with stirring overnight (18 hrs). The precipitated crystals were sucked off and washed with 500 ml of MTBE.

91.2 % of theory of clopidogrel hydrobromide were obtained, which has been characterized by an X-ray diffraction pattern as Form II. HPLC purity more than 99.5 %.

Melting points were measured at Kofler's block. The diffraction pattern was obtained by means of X'PERT PRO MPD PANalytical diffractometer.

CLAIMS

1. A method of preparation of clopidogrel hydrobromide of crystalline Form II characterized in that clopidogrel base is dissolved in an organic solvent and precipitated with gaseous hydrogen bromide, and, optionally, the resulting clopidogrel hydrobromide is further dissolved and crystallized from a solvent comprising a C_1-C_5 alcohol or a mixture of a C_1-C_5 alcohol with an ether, ester or ketone.

2. The method according to claim 1 characterized in that clopidogrel hydrobromide is precipitated from an organic solvent selected from the group of C_6-C_{12} aromatic hydrocarbons.

3. The method according to claim 1 characterized in that precipitation is carried out at a temperature of -15 °C to 30 °C and growth of crystals occurs at a temperature lower than 10 °C.

4. The method according to claim 1 characterized in that a solution of the clopidogrel base having a concentration of 1 to 40 % is used, the molar ratio of the clopidogrel base and hydrogen bromide being 1 : 0.9 to 1.1.

5. The method according to any of the preceding claims, characterized in that gaseous hydrogen bromide is introduced into a solution of the clopidogrel base having a concentration of 15 to 40 %.

6. The method according to any of claims 1-3 characterized in that gaseous hydrogen bromide is introduced into a solution of the clopidogrel base having a concentration of 1 to 10 %, clopidogrel hydrobromide of Form III thus being precipitated, which is further crystallized from a C_1-C_5 alcohol or a C_1-C_{15} alcohol in an admixture with an ether, ester or ketone.

7. The method according to claim 5 characterized in that clopidogrel hydrobromide of Form II is crystallized from a mixture of a C_1-C_5 alcohol and an ether.

8. The method according to claim 6 characterized in that clopidogrel hydrobromide of Form II is crystallized from a mixture of 2-propanol and methyl *tert*-butyl ether.

9. Clopidogrel hydrobromide of Form III, characterized with peaks ascertained by X-ray diffraction in the following 2θ positions: 7.796 °; 15.380 °; 18.389 °; 19.369 ° and 23.895 °.

10. Use of clopidogrel hydrobromide of Form III according to claim 9 for the preparation of clopidogrel hydrobromide of Form II, applicable as a pharmaceutical active substance.

Abstract

Title of Invention: Method of producing crystalline clopidogrel hydrobromide

A method of preparation of clopidogrel hydrobromide of crystalline Form II, wherein clopidogrel base is dissolved in an organic solvent, preferably a C_6-Cl_2 aromatic hydrocarbon, and precipitated with gaseous hydrogen bromide, and, optionally, the resulting clopidogrel hydrobromide is further dissolved and crystallized from a solvent comprising a C_1-C_5 alcohol or a mixture of a C_1-C_5 alcohol with an ether, ester or ketone. Clopidogrel hydrobromide of Form III, characterized with peaks ascertained by X.-ray diffraction in the following 2θ positions: 7.796 °; 15.380 °; 18.389 °; 19.369 ° and 23.895 °, and use thereof for the preparation of Form II of clopidogrel hydrobromide.

Clopidogrel hydrobromide – Form III

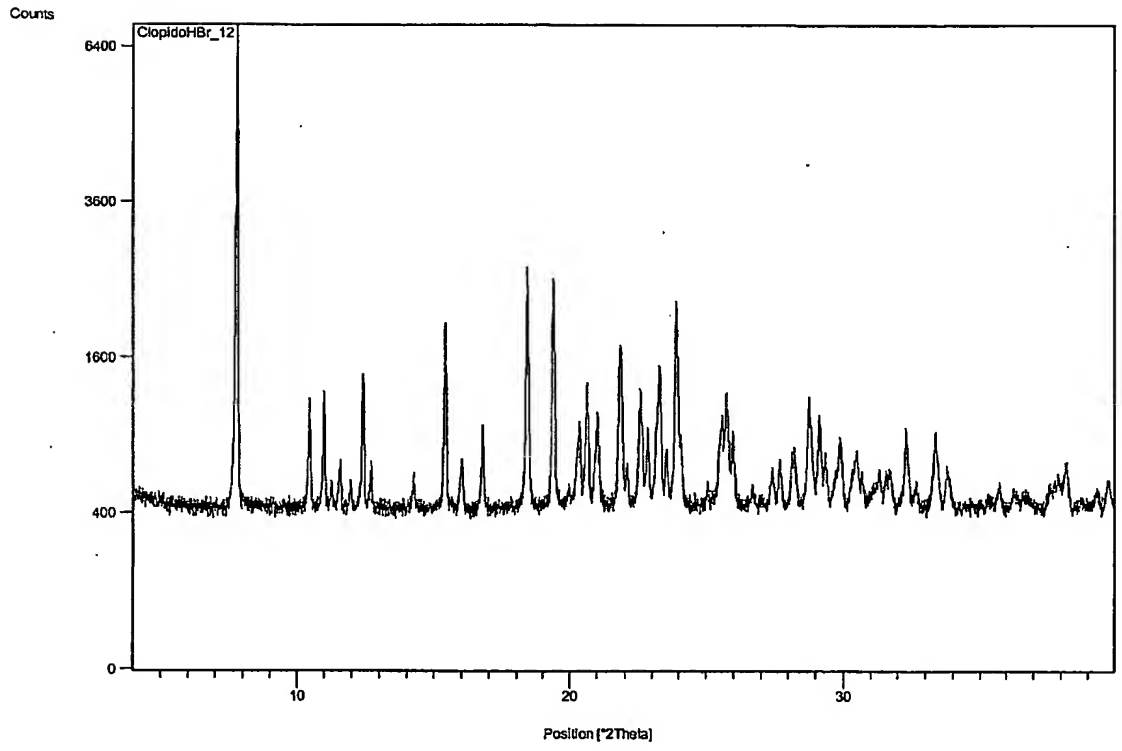


Fig. 1

Ref. No. 4311 / 04

I, undersigned, certify by these presents, with reference to my status as the permanent sworn interpreter of the English language, appointed by the decree of the Ministry of Justice of the Czech Republic, dated November 5, 1985, Ref. No. ZT 1941/85, that the above is the true and exact translation of the Czech text of the annexed document.

Prague, December 18, 2004

JUDr. Jaromír VOLNÝ
překladatel jazyka anglického, německého

JUDr. Jaromír V o l n ý
Sworn interpreter